thiouracil and the other potassium perchlorate. The antithyroid activity of both drugs was assessed by the time taken for the index to fall within the range 0 to 5. Estimations of the basal metabolic-rate confirmed that at this level patients were euthyroid. The time taken to reach the euthyroid state was independent of the initial severity of the disease. In 33 of 40 patients the rate of therapeutic response bore a linear relationship to time. Methylthiouracil in doses of 600 mg. a day for three weeks followed by doses of 300 mg. a day was shown to be a more effective antithyroid drug than potassium perchlorate in doses of 600 mg. a day. A " cross-over " test carried out on 14 patients, who had relapsed after a first course of treatment, confirmed this conclusion.

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## A COMPARISON OF POTASSIUM PERCHLORATE, METHYLTHIOURACIL, AND CARBIMAZOLE IN THE TREATMENT OF THYROTOXICOSIS

J. CROOKS
M.D. Glasg., M.R.C.P., M.R.C.P.E., F.R.F.P.S.
SENIOR REGISTRAR IN MEDICINE

E. J. WAYNE
M.D. Leeds, F.R.C.P., F.R.F.P.S.
REGIUS PROFESSOR OF PRACTICE OF MEDICINE

UNIVERSITY DEPARTMENT OF MEDICINE, GARDINER INSTITUTE, WESTERN INFIRMARY, GLASGOW

AT some time during the course of their disease the majority of patients with thyrotoxicosis receive an antithyroid drug. It is probable that these substances provide the most satisfactory form of treatment for most young patients and the speed and certainty of their action often make their immediate administration necessary even when it has been decided subsequently to use an alternative form of treatment. It is obviously of importance to know which is the most effective and the safest member of the group. The ideal antithyroid drug should be rapid in its action and should produce no adverse side-effects. In this country the two most commonly used drugs are methylthiouracil and carbimazole. In other countries propylthiouracil and methimazole are popular. All, however, occasionally produce toxic effects, of which agranulocytosis is the most serious since it may prove fatal. The most common adverse reaction is the drug rash, but nausea, drug fever, aplastic anæmia, thrombocytopenia, conjunctivitis, and lymph-gland enlargement have all been reported.

Methylthiouracil was first introduced in 1944 and was for long the standard antithyroid substance in use in this country. Carbimazole received favourable reports in 1953 from Doniach and from Poate. It was said to produce fewer side-effects than methylthiouracil although its action was slower. Its use has tended to increase especially since evidence that it is less toxic was produced by Greene and Morgan (1956) and by Burrell et al. (1956). It is said to be ten times as active as methylthiouracil and is usually given in one-tenth of the dose. The *British Pharmacopœia* recommends that the controlling dose of methylthiouracil should be from 0·2 to 0·6 g. daily and of carbimazole from 30 to 60 mg. daily.

Potassium perchlorate is a rival and more recent antithyroid drug with a different type of action. Unlike the thiouracils and imidazoles which prevent the iodination of tyrosine, it acts by inhibiting the iodide-trapping mechanism of the thyroid gland. As a simple inorganic compound it would seem a priori to be less likely to produce sensitisation effects than the organic antithyroid substances, and in particular to be less likely to damage the hæmopoietic system. It was first shown to be a suitable substance for clinical use by Godley and Stanbury (1954). This was confirmed in a much larger series of cases by Morgans and Trotter (1954) who found that the rate of response produced by 400 mg. daily was less than that produced by methylthiouracil in a dose of 200 mg. daily.

Shortly after their report was published we decided to assess the relative merits of potassium perchlorate, methylthiouracil, and carbimazole. We shall present our conclusions based on a study of more than 450 patients. It soon, however, became evident that while the comparative incidence of the side-effects of these substances would be revealed by this investigation a comparison of their relative efficacy presented a more difficult problem. For this reason we devised a clinical method of comparing antithyroid drugs based on the allocation of points to those features of thyrotoxicosis which are reversible by therapeutic measures. This enabled us to derive a " therapy index " which could be followed from week to week and the time taken for it to reach and remain at a value of 5 or lower could be used as a measure of the effectiveness of the form of treatment. We have already recorded in illustration of our method a comparison of the effect of 600 mg. daily of potassium perchlorate with that of methylthiouracil in doses of 600 mg. daily for two weeks followed by 300 mg. daily. Using these dosage schemes methylthiouracil was more effective (Crooks et al. 1960). It seemed to us probable that this result depended on the relative doses used and a further series of cases has been studied using 1000 mg. of potassium perchlorate daily. Since our clinical experience had led us to doubt the statement that carbimazole is, weight for weight, ten times as active as methylthiouracil we also compared these two substances.

Potassium perchlorate proved to be both effective and relatively free from side-effects and we now use it routinely. We have, therefore, studied more closely some of its alleged disadvantages notably the tendency for its activity to be affected by variations in the dietary intake of iodine and its liability when used before operation to produce an unduly vascular gland. We also report the results of its use in pregnant patients with thyrotoxicosis.

### Material and Methods

We have studied two further groups of 20 cases in addition to the two already reported (Crooks et al. 1960).

All the patients had diffuse goitres and exophthalmos and thus were examples of classical Graves's disease. To one group carbimazole was given in doses of 20 mg. three times a day for two weeks followed by 10 mg. three times a day (i.e., one-tenth of the dose of methylthiouracil which was used in our previous series). Potassium perchlorate was given to the other group in a dose of 200 mg. 5 times a day. The dietary intake of iodide was not restricted.

The method of comparison was that used in the earlier series except that estimations of basal metabolic-rate (B.M.R.) were made only at the end of the investigation to confirm that the patients were euthyroid.

TABLE I—DISTRIBUTION OF PATIENTS IN SERIES 3 RECEIVING CARBIMAZOLE AND POTASSIUM PERCHLORATE (1000 MG. DAILY) SHOWING TIME TAKEN TO EFFECT "CURE"

| Time to effect "cure" (weeks) | Carbimazole (no. of patients) | Potassium perchlorate (1000 mg. daily) (no. of patients) |
|---|---|---|
| 3–4 | .. | .. |
| 5–6 | .. | 8 |
| 7–8 | 7 | 3 |
| 9–10 | 2 | 4 |
| 11–12 | 4 | 1 |
| 13–14 | 3 | 2 |
| 15–16 | .. | 1 |
| 17–18 | 2 | .. |
| 19–20 | .. | 1 |
| 21–22 | 2 | .. |
| Total | 20 | 20 |
| Mean time to "cure" | 12·3 weeks | 9·4 weeks |

The study of the comparative toxic effects of these substances is based on observations made on 486 patients seen and treated by us in our wards or clinic. After reference to their general practitioner they continued to attend hospital from time to time so that the occurrence of toxic effects could be accurately recorded.

## Results

### "*Therapy Indices*"

The times taken to effect "cure" for both drugs are shown in table I. The mean time to "cure" of the 20 patients on carbimazole was 12·3 weeks and the corresponding figure for potassium perchlorate was 9·4 weeks.

Table II gives the mean times to "cure" of the groups treated with methylthiouracil, carbimazole, and potassium perchlorate in doses of both 600 mg. and 1000 mg. daily.

For the purpose of statistical analysis the drugs have been represented by the letters A, B, C, and D as shown in the table. An analysis of variance on the 80 patients studied shows that there are significant differences between the mean values for A, B, C, and D. In particular A is significantly different from B and C ($P<0·05$); D is significantly different from B and C ($P<0·05$); and there was no significant difference between A and D. A further analysis of variance was carried out on the 60 patients remaining after the exclusion of those who had been given methylthiouracil. It was found that there was a significant difference between B and D ($P<0·05$); a significant difference between C and D ($P<0·05$); and no significant difference between B and C.

TABLE II—MEAN TIMES TO EFFECT "CURE" FOR METHYLTHIOURACIL, POTASSIUM PERCHLORATE, AND CARBIMAZONE

| | Drug | Time to effect "cure" (weeks) |
|---|---|---|
| A | Methylthiouracil .. .. .. .. | 9·1 |
| B | Potassium perchlorate (600 mg. daily) .. | 13·1 |
| C | Carbimazole .. .. .. .. | 12·3 |
| D | Potassium perchlorate (1000 mg. daily) .. | 9·4 |

These results can be summarised as follows: methylthiouracil in doses of 600 mg. daily for 2 weeks followed by 300 mg. daily and potassium perchlorate (1000 mg. daily) were equally effective as measured by the time taken to effect "cure", while both were more effective than carbimazole in one-tenth of the dose of methylthiouracil or potassium perchlorate (600 mg. daily).

### *Effect of Variations in the Intake of Iodine on Potassium Perchlorate Therapy*

Potassium perchlorate affects the iodide-trapping mechanism of the thyroid and it is known that the goitrogenic action of substances with this action can be overcome if sufficient iodide is given (Franklin et al. 1944). In our earlier series we advised patients given potassium perchlorate 600 mg. daily, to restrict their iodine intake by excluding fish from the diet, by using uniodised salt, and by avoiding medicines.

Diet histories from 8 patients and urinary assays from 20 patients revealed a great variation in the degree to which iodide restriction had been achieved. The therapeutic responses to potassium perchlorate of patients with relatively high and low intakes were statistically analysed and no difference was found. In our later observations therefore we have urged no dietetic restrictions and have merely advised patients to avoid certain cough medicines which contain iodide in relatively large quantities.

### *Preoperative Use of Potassium Perchlorate*

It is generally agreed that antithyroid drugs should be used to prepare a thyrotoxic patient for partial thyroidectomy. The usual method is to bring the disease under control with one of the organic antithyroid drugs and then to give iodide for 10–14 days before operation. It is said that this renders the gland less vascular and diminishes the likelihood of postoperative thyroid crises.

Godley and Stanbury (1954) prepared 13 patients for operation with potassium perchlorate and stated that the consensus of opinion of the operating surgeons was that a few of the glands were more vascular than those of patients prepared with propylthiouracil and iodine. 2 patients who before operation received iodide in addition to perchlorate escaped from control. For this reason Morgans and Trotter (1954) did not use perchlorate in those patients who were likely to require partial thyroidectomy.

We have prepared 20 patients for operation with potassium perchlorate alone. 18 of these patients had small nodular glands and the surgeon did not find more technical difficulty due to increased vascularity of the gland than after conventional preparation.

Opinions as to the degree of vascularity must of necessity be highly subjective. It may well be that contradictory views on the effects of the antithyroid drugs on vascularity are due to variation in the selection of cases and to the lack of an investigation designed so as to eliminate the effects both of biological variation and of bias on the part of the surgeon. The blocking effect of potassium perchlorate on thyroid hormone synthesis continues for some time after the drug has been withdrawn and administration can cease at the time of operation.

### *Use of Potassium Perchlorate During Pregnancy*

Opinion is almost unanimous that the most appropriate form of therapy for women who develop thyrotoxicosis during pregnancy is the administration of an antithyroid drug. Goitre and hypothyroidism have been reported in the infants of mothers who have received these substances but it is rare, and when it occurs the dosage has almost always been unduly high (Macgregor and Goodwin 1953). We have treated 12 pregnant thyrotoxic patients with potassium perchlorate and in each have achieved satisfactory control of the disease. One of the infants had a very slight enlargement of the thyroid gland which disappeared within 6 weeks. The remainder showed no abnormality of any kind. We report these results to show that the different mode of action of potassium perchlorate and its special physical properties do not render it more liable to affect the fœtal thyroid than the antithyroid substances in more common use.

### *Toxic Effects of Antithyroid Drugs*

We have treated 486 patients with either methylthiouracil, carbimazole, or potassium perchlorate sufficiently long to be able to assess their relative tendency to give rise to toxic side effects. Table III shows the results. No statistically significant difference was

TABLE III—TOXIC EFFECTS

| Toxic effect | Methylthiouracil (600 mg. daily 2 wks., then 300 mg. daily) | Carbimazole (60 mg. daily 2 wks., then 30 mg. daily) | Potassium perchlorate | |
|---|---|---|---|---|
| | | | 600 mg.* or 1000 mg. | 1500 mg.† or 2000 mg. |
| No. of cases | 151 | 85 | 200 | 50 |
| Skin rashes | 5 | 4 | 1 | 5 |
| Nausea | .. | 1 | 3 | 2 |
| Drug fever | 2 | .. | .. | .. |
| Agranulocytosis | 2 | 2 | .. | 1 |
| Thrombocytopenia | 1 | .. | .. | .. |

* 35 patients. † 10 patients.

between the liability of the organic substances to produce sensitisation reactions such as skin rashes or blood dyscrasias. Potassium perchlorate, on the other hand, in doses of 1000 mg. a day or under was less likely than the organic antithyroid compounds to produce adverse effects of this type. Higher doses of potassium perchlorate produced reactions as frequently as the organic compounds.

The rashes produced by potassium perchlorate were maculopapular and were confined to the extremities except in 1 patient in whom the rash was generalised. This patient had an associated pyrexia and marked desquamation followed the disappearance of the eruption. In 3 of the 6 cases the rash subsided although the administration of the drug was continued.

The patient with agranulocytosis was a young woman receiving 1500 mg. of potassium perchlorate a day. During the third week of treatment she developed a sore throat, pyrexia, and generalised muscular pain. Blood examination showed a total polymorphonuclear leucocyte count of 750 per c.mm. The peripheral blood was otherwise normal and the bone-marrow showed no evidence of a maturation defect of the white-cell series. Administration of the drug was stopped and the leucocyte count rose rapidly to normal levels. The patient had received no other drugs which might have caused leucopenia.

The rashes produced by the organic antithyroid compounds were all maculopapular. This is a type of eruption which is well known to occur in those who become sensitised to this series of compounds. Urticaria which has also been reported was not observed in this series.

4 patients complained of nausea while taking potassium perchlorate. 3 of them were able to continue taking the drug when an antacid mixture was given along with it and the nausea disappeared within a week. The fourth refused further treatment.

## Discussion

The "therapy index" has been used to assess the rate of improvement in four different groups of patients suffering from classical Graves' disease. One group received carbimazole, one methylthiouracil, and the other groups potassium perchlorate in two different doses. From these investigations we are able to draw two conclusions. First, carbimazole is less effective than methylthiouracil when given in one-tenth of the dose. Secondly, potassium perchlorate is more effective in high than in low dosage.

The very extensive literature on the antithyroid drugs is fully reviewed by McGavack (1951), Werner (1955), and Crooks (1957), and it is clear that the four drugs most widely used at present are methylthiouracil, propylthiouracil, methimazole, and carbimazole. All are effective and relatively safe. The particular substance used by any given physician seems to be determined by two factors. In the first place it is clear that the country of origin is important since methylthiouracil and carbimazole were both first synthesised and marketed in Europe whereas propylthiouracil and methimazole were originally American products. The second factor of importance is the relative conservatism of the individual clinician. Most physicians see no reason to try a new remedy if the existing one is satisfactory although some are impressed by new substances even if their advantages are marginal. Moreover, any clinician tends to be overimpressed by an example of a patient under his care who shows a serious side-effect even though the statistical hazards of this occurrence can be shown to be small. Against this background of national and individual prejudice there is almost no statement which has not been made about the relative effectiveness, speed of action, and toxicity of these drugs.

We have found no published observations on the relative dosage of antithyroid drugs which cannot be explained on the view that the response of a patient to an antithyroid drug is a function of the dose. At a certain critical level a dose is reached at which synthesis of the thyroid hormone is completely blocked. Inspection of curves showing the effect of different doses of methylthiouracil on the uptake of radioactive iodine by the gland, as reported, for example, by Goodwin et al. (1949), illustrate this phenomenon.

The first problem in dealing with the dose of an antithyroid drug is to discover the least dose which in the majority of patients will effectively block secretion of the thyroid hormone during each 24 hours. This is probably of the order of 450 mg. for methylthiouracil, 60 mg. for carbimazole, and 1000 mg. for potassium perchlorate. The question then arises of the relative liability of these drugs to produce toxic side-effects. In spite of their importance we know relatively little about sensitisation reactions to drugs. It is not possible, for example, to say with certainty whether they are dependent on dose. With some drugs (e.g., amidopyrine) a single dose may produce a reaction in a sensitised patient. With others, such as chloramphenicol or the sulphonamides, there seems to be a tendency for reactions to be related to total dosage. In the case of the antithyroid substances the balance of evidence seems to suggest that they belong to the latter type (Lehr 1948). Certainly our own results show that potassium perchlorate produces more reactions in high than in low dosage. It seems therefore to us that it is unjustifiable to group together series of cases collected from the literature without allowing for this factor of dosage and without applying statistical tests of significance to all the results reported. The two published comparisons of carbimazole and methylthiouracil (Burrell et al. 1956, Greene and Morgan 1956) are thus rendered inconclusive.

Our tentative conclusions are these. There is no convincing evidence that any of the organic antithyroid drugs is significantly more toxic than any other when it is given in therapeutically equivalent dosage. Our experience suggests that potassium perchlorate is less liable to give rise to skin rashes or blood dyscrasias in doses which act as quickly as the conventional therapeutic doses of methylthiouracil and carbimazole.

Potassium perchlorate thus appears to us to be the antithyroid drug of choice. A few observers other than Godley and Stanbury (1954) and Morgans and Trotter (1954) have used it and found it satisfactory. Thus Kleinsorg and Krüskemper (1957) treated 47 cases with doses of 1·6 to 2·0 g. a day; 2 patients developed a rash. Buttaro and Brunori (1955) reported 25 patients successfully treated with doses of 600 mg. a day and 1 developed a skin rash. Observations in our series showed that it is

unnecessary to restrict the dietetic intake of iodine during the administration of potassium perchlorate. In our experience this drug can be satisfactorily used for pre-operative preparation when the gland is small and nodular. Whether or not it can be used in this way when the gland is large requires further investigation.

Sensitisation to potassium perchlorate can occur. The usual manifestation is a rash which usually subsides quickly even if administration is continued. It is much more likely to develop when the dosage is high. Our single case of agranulocytosis occurred in a patient receiving large doses of the drug but if the use of potassium perchlorate increases we should not be surprised to learn that this serious condition may be associated with lower doses or that the bone-marrow may be affected in other ways. The balance of present evidence, however, is in favour of its very low toxicity. It has the additional merit of being very cheap and it is of some interest that the only proprietary preparation of potassium perchlorate was for many years in category 5 of the List of Proprietary Medicines Classified by the Joint Committee on Prescribing which is published jointly by the Ministry of Health and the Department of Health for Scotland.

**Summary**

A clinical method of assessing the rate of improvement of groups of patients suffering from thyrotoxicosis has been applied to four series of cases receiving respectively methylthiouracil, carbimazole, and potassium perchlorate in two different doses. Carbimazole was less effective than methylthiouracil when given in one-tenth of the dose. Potassium perchlorate in high dosage was as effective as methylthiouracil and more effective than carbimazole and smaller doses of perchlorate.

Four larger series of patients receiving these drugs were studied to ascertain the incidence of toxic side-effects. Potassium perchlorate in a daily dose of 600–1000 mg. produced fewer side-effects than when it was given in daily doses of 1·5–2·0 g. The lower dosage range also gave rise to fewer side-effects than either methylthiouracil or carbimazole in therapeutically equivalent doses. No statistical difference in the incidence of sensitisation reactions was found between the latter two substances.

Potassium perchlorate in high doses is liable to produce skin rashes, and in 1 of our cases agranulocytosis developed.

It is not necessary to restrict the dietary intake of iodine during perchlorate administration. It can be used to prepare patients for thyroidectomy when the gland is small and nodular and can also be used during pregnancy. Potassium perchlorate, 1000 mg. daily in divided doses, is the antithyroid drug of choice in the medical treatment of thyrotoxicosis.

We wish to thank Dr. R. A. Robb, Mitchell lecturer in statistics, University of Glasgow, for help with the statistical aspects of this work, and Mr. D. H. Clark, F.R.C.S., who carried out the thyroidectomies to which we refer.

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# THE INCREASE IN DIFFUSING CAPACITY OF THE LUNGS ON EXERCISE

## AN EXPERIMENTAL AND CLINICAL STUDY

J. MACNAMARA
M.D. N.U.I., M.R.C.P.
F. J. PRIME
M.D. Durh.
SENIOR LECTURER IN PHYSIOLOGY
J. D. SINCLAIR
M.D. N.Z., M.R.A.C.P.
*From the Department of Physiology, Institute of Diseases of the Chest, Brompton, London, S.W.3*

WHEN oxygen is taken up from the alveoli of the lungs it has to penetrate the mechanical barrier of the tissue elements and fluids separating it from the molecules of hæmoglobin in the red cells, the process is one of simple physical diffusion. Methods of measuring the permeability of this barrier to gases have been elaborated which permit an estimate of the so-called *diffusing capacity* of the lungs. The simplest of these uses carbon monoxide as the test gas, and measures its rate of absorption in the steady state (Bates, Boucot, and Dormer 1955). The measured rate of uptake of this gas in low concentration in an inspired gas mixture is divided by its mean alveolar concentration during the test (expressed as partial pressure) to give a result in ml. per min. per mm. Hg. On physical principles, it may be assumed that the diffusing capacity thus measured is proportional to the area of the diffusing surface and varies inversely with its thickness. Normal results vary between 15 and 25 ml. per min. per mm. Hg at rest and from 25 to 40 ml. during exercise. Experience in the past few years in many centres has shown how valuable measurements of diffusing capacity are clinically; moreover, many facts of physiological interest and importance have been revealed by them. Among the latter is the observation, repeatedly confirmed, that the diffusing capacity is greatly increased during exercise. The object of this communication is to report some investigations which throw light on the way in which this change is brought about.

### Investigations and Conclusions

In an experimental assessment of the steady-state method of measuring pulmonary diffusing capacity using carbon monoxide (MacNamara, Prime, and Sinclair 1959) we drew attention to the fact that the results obtained were significantly dependent on the minute-volume of respiration during the test. This finding made us wonder whether the apparent increase in diffusing capacity on exercise was due entirely to the effects of hyperventilation. We therefore measured the diffusing capacity in four healthy subjects at rest during voluntary hyperventilation at various rates. We found that the diffusing capacity rose steadily with increasing ventilation, showing no definite tendency to a maximum value within the range of voluntary hyperventilation which it was possible to maintain for the time required for the test. These results were compared with values of diffusing capacity in the same subjects, measured at various rates of exercise, by plotting both sets of values on a graph relating them to pulmonary ventilation. Contrary to our expectation, we found that the curves plotted from the exercise values did not coincide with those for voluntary hyperventilation but lay above them. A typical comparison in one subject is shown in the figure. This discovery has since been confirmed by results published by two groups working